

Division of Kidney, Urologic and Hematologic Diseases

Josephine P. Briggs, M.D.
Director

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5001 EPIDEMIOLOGY OF UROLOGIC DISEASES IN AMERICA (RFP DK-00-005)

FY 2001 Action

The NIDDK issued a Request for Proposal (RFP NIH-NIDDK-00-05 on or about July 6, 2000 and listed on the NIH Guide as notice DK-00-004 on July 17, 2000) seeking an organization or an institution to compile a compendium, which is identified as "Urologic Diseases in America" (UDA).

Background

No single data source exists that describes and evaluates the scope of practice of the specialty of urology, including disease incidence, morbidity, mortality, outcome, economic health impact, and practice patterns. Such information is essential to permit the NIH to effectively and efficiently plan future research in urology as well as to address issues important to other governmental agencies. The NIDDK has developed an RFP soliciting applications for the Urologic Diseases in America project. This solicitation is in response to language from the National Kidney and Urologic Diseases Advisory Board which stated: "The Board believes that NIDDK should assume a more significant role in the analysis and dissemination of information on urologic disease to permit early recognition of important research," and to Congressional Appropriations language which stated: "The committee recommends that the NIDDK consider developing an appropriate database for urologic diseases. This database would, for the first time, give realistic estimates of the extent of these diseases, the health care expenditures for these diseases, the variations in treatment, and the effect that these diseases have on minority populations."

Research Goals and Scope

The Urologic Diseases in America compendium will delineate the changes in the epidemiology, health economic impact, and practice patterns for each of the diseases currently included within the scope of practice of the specialty of urology, analyzed retrospectively over a ten-year period. The UDA compendium will consist of data tables and analyses as well as narrative descriptive chapters that amplify the data analyses.

The objectives of the Urologic Diseases in America project will include data collection and analyses of the following specific topics: (1) changes in the overall health care burden for individual urologic diseases; (2) changes in physician practice patterns for each urologic disease; (3) changes in demographics of persons with urologic diseases; (4) the impact of specific urologic diseases, especially diseases of the prostate, on the minority populations of the U.S.; and (5) the documentation of new and evolving therapies for urologic diseases and their potential impact on treatment outcomes and health care costs.

5002 RESEARCH IN STUDIES ON HEREDITARY STONE DISEASE (PA 00-091)

FY 2001 Action

The NIDDK has released a Program Announcement (PA-00-091, published in the NIH Guide on April 27, 2000) to encourage submissions of R21 and R01 applications for pilot and feasibility studies that utilize new and innovative approaches to the study of hereditary stone diseases. The Division of Kidney, Urologic and Hematologic Diseases of the NIDDK has set aside specific funds to support this Program Announcement.

Background

Urinary tract stone disease constitutes a major health care burden for the U.S. population. Calcium oxalate is the major constituent of these urinary tract stones. Studies suggest that a subset of persons who have chronic, recurrent urinary tract stone disease have a familial predisposition to the disease. The etiology and the genetic abnormality in these persons are not known. However, there is a group of individuals with known inherited disorders who develop recurrent calcium oxalate stones at a very early age. These persons have a genetic metabolic disorder known as primary hyperoxaluria, in which a genetic defect causes excessive excretion of oxalate in the urine. These primary hyperoxaluria disorders have been shown to be due to a defect in the regulation of oxalate synthesis in the liver, resulting in an accumulation of excess oxalate. The purpose of this Program Announcement is to increase investigator interest in research into the genetics and heritability of oxalate regulation and the oxalate stone diseases.

Research Goals and Scope

Although calcium oxalate stone disease is a very common health problem in the U.S., there is very little new, innovative research being applied to the understanding of the etiology, risk factors, or genetic basis of this chronic disease. This announcement focuses on the heritable oxalate stone disorders in an attempt to better understand the metabolic and genetic defects responsible for the disease and to eventually develop more effective treatment and preventive strategies. The calcium oxalate stone disease that is most commonly identified in adults is poorly understood from a basic science point of view. It is known that this disease tends to occur within families, but pedigrees have not been well established or studied.

A rare, heritable cause of nephrolithiasis has been identified and characterized. This disorder results in the onset of oxalate stone disease early in childhood and can frequently lead to renal failure. Primary hyperoxaluria is due to a defect in the liver peroxisomes of the enzyme alanine-glyoxylate aminotransferase (AGT), which catalyzes the transamination of glyoxylate to glycine. The non-catalyzed glyoxylate is oxidized to oxalate and is excreted in excess in the urine. To address these issues and others related to calcium oxalate stone disease, the following are some areas in which it is suggested that applications be submitted: (1) develop strategies to replace the gene defect in oxalosis and

hyperoxaluria; (2) develop strategies for development of new animal models for the study of the calcium oxalate stone diseases; and (3) develop strategies to assemble and investigate family pedigrees with calcium oxalate stone disease for risk factors, genetic defects, and other related factors.

5003 EPIDEMIOLOGY OF CHRONIC PELVIC PAIN OF THE BLADDER AND INTERSTITIAL CYSTITIS (RFA DK-00-018)

FY 2001 Action

The NIDDK issued a Request for Applications (RFA) in FY 2000 to establish a multi-center collaborative study of the epidemiology of chronic pelvic pain of bladder origin and interstitial cystitis.

Background

Interstitial cystitis is one of a constellation of diseases and disorders that are characterized by chronic pelvic pain associated with bladder symptoms of urinary frequency and urgency. Although there have been several published studies on the epidemiology of interstitial cystitis, they have focused almost totally on women and on non-minority populations, and have been limited in scope. Chronic pelvic pain of bladder origin is a symptom complex found in children and adults of all ages. The frequency of this symptom complex is uncertain, with estimates varying widely. The long term health impact and associated health care costs are unknown. The only analyses of incidence and prevalence available are based on health care records that do not accurately establish the incidence of the symptom complex. No epidemiological studies of the broader symptom complex of chronic pelvic pain of bladder origin have been conducted to date.

Research Goals and Scope

The purpose of this Request for Applications (RFA) is to conduct a multi-institution, collaborative epidemiological study of chronic pelvic pain of the bladder and interstitial cystitis. The goals of this study are to determine the prevalence, incidence, risk factors, quality of life and functional status, and health resource utilization for interstitial cystitis and chronic pelvic pain of bladder origin in men, women, and children. A unique feature of this RFA is the plan to utilize ongoing prospective cohort studies, clinical trials, and large patient databases to obtain baseline and follow-up information. An important goal of this project will be the development of common definitions of these symptom complexes so that data can be combined across study sites.

5004 PROSPECTIVE STUDY OF CHRONIC RENAL INSUFFICIENCY (RFA DK-01-005)

FY 2001 Action

The NIDDK will establish a multi-center prospective cohort study of patients with chronic renal insufficiency to study the factors associated with rapid decline in renal function and to identify risk factors for cardiovascular disease. In addition, a central repository for biological specimens, including genetic material, will be established and serve as a resource for studies in this area.

Background

End-stage renal disease (ESRD) is an important medical and public health problem in the U.S. that disproportionately affects racial and ethnic minority groups. The increase in the number of ESRD patients is due mainly to an increase in the number of patients with renal disease caused by diabetes. In patients with ESRD, cardiovascular disease is the leading cause of death, and a better understanding of the risk factors for this disease burden is required before interventions can be evaluated and implemented. While numerous epidemiological studies have been conducted in patients with ESRD leading to improved care and better quality of life, few studies have been performed in patients with chronic renal disease prior to reaching ESRD, during a period of chronic renal insufficiency. Of the small number of studies conducted, all of them have significant methodological shortcomings. Thus, our knowledge about the factors that influence decline in renal function and development of cardiovascular disease in patients with chronic renal insufficiency is rudimentary.

Prospective cohort studies have played an important role in defining risk factors for a wide range of diseases and it is envisioned that data and patient specimens obtained from this cohort study will serve as a national resource for investigations of chronic renal disease and cardiovascular disease.

Research Goals and Scope

The objective of this RFA is to establish a prospective, multi-ethnic, and racial cohort study of approximately 3,000 patients with chronic renal insufficiency to determine the risk factors for rapid decline in renal function and development of cardiovascular disease. Establishing a cohort of patients with chronic renal insufficiency, with cause of renal disease similar to that observed in the U.S. ESRD patient population, and following them prospectively will also provide an opportunity to examine genetic, environmental, behavioral, nutritional, quality of life, and health resource utilization factors in this patient population.

5005 HEMATOPOIETIC STEM CELL PLASTICITY

FY 2001 Action

A research solicitation will be issued, in collaboration with the National Heart, Lung, and Blood Institute to encourage applications to promote the thorough exploration and characterization of the plasticity of adult-derived hematopoietic stem cells.

Background

The field of stem cell biology has undergone a dramatic shift in perspective over the past two years due to a number of publications indicating that adult tissues may harbor stem cells that can differentiate into a wider variety of cell types than previously appreciated. Although it has been recognized for a long time that many adult tissues contain stem cells capable of regenerating cell types native to that tissue, it was thought that the differentiation of such stem cells was limited to cell types of that tissue. Recent publications, however, have indicated a remarkable plasticity of adult tissue-derived stem cells, opening the possibility of developing myriad new strategies for cell and gene therapy. The discovery of multi-potential adult-derived stem cells offers the possibility of bypassing the use of human embryonic stem cells with the attendant ethical concerns.

Despite this change in thinking and the promise of the field, few data support the initial published observations, and almost no studies have been undertaken of the underlying mechanisms or biology of the system. The ability to purify and *ex vivo* culture and manipulate totipotent stem cells from non-embryonic origin would provide investigators with an invaluable cell source to study cell and organ development. In addition, such cells would be extremely useful for the development of "replacement" tissues for congenital or degenerative disorders.

Research Goals and Scope

The surface phenotype of bone marrow-derived cell populations capable of the reconstitution of lethally irradiated recipients needs to be characterized, and the potential of bone marrow and organ tissue or organ-derived populations to give rise to specific non-hematopoietic cell types after bone marrow transplantation (BMT) determined. Isolation of stem cell populations that are capable of giving rise to both hematopoietic cells and cells of other types after BMT in appropriate *in vivo* models will be encouraged, and the mechanisms of engraftment of non-hematopoietic tissues examined.

The role of local environmental stimuli on the ability of transplanted stem cells to give rise to non-hematopoietic stem cells should be determined in adult non-hematopoietic tissues of interest, including muscle, brain, heart, kidney, and liver. An evaluation is needed of the developmental potentials of both bone marrow and other putative adult stem cell populations. Information is needed to understand the nature of the biological cues for differentiation, and how to manipulate the cells and the host in order to facilitate production of desired cell types after stem cell transplantation. Different transplantation

models are needed that may reveal the ability of different cell types to provide for hematopoietic cell engraftment. Since the nature of a cell can not be established definitively simply on the basis of origin from a particular location, a defined population, or possession of a particular phenotype, the definitive way to determine the potential of a cell is to address it clonally. Thus, cloning, limiting dilution, insertion marking, or other techniques that will elucidate the repertoire of stem cells, should be used to determine proof of plasticity. Since many other systems may also occasionally export stem cells to the circulation and to diverse tissues, measurement of non-hematopoietic tissues for hematopoietic potential is needed.

5006 FAMILY INVESTIGATION OF NEPHROPATHY AND DIABETES: CELL IMMORTALIZATION

FY 2001 Action

The NIDDK plans to expand the Family Investigation of Nephropathy and Diabetes (FIND) study to create a sample repository and to create immortalized cell lines from each recruited subject as a renewable resource for DNA for genetic analyses.

Background

The FIND study was funded September 30, 1999, as a Cooperative Agreement (UO1) as a result of RFA DK-99-005. The aims of the FIND consortium are to identify genetic loci and ultimately genes that influence susceptibility to and severity of diabetic nephropathy in Caucasian, African American, Hispanic, and Native American populations across the U.S. The Study Consortium consists of eight Participating Investigative Centers (PICs) and a Genetic Analysis and Data Coordinating Center.

Investigation of polygenic disease requires large samples and integration of results across many studies. The External Advisory Committee for FIND has reviewed the proposed protocol and advises the NIDDK to take appropriate steps to insure that results can be replicated and integrated with other genetic studies of diabetic nephropathy. Their advice to the NIDDK has included the recommendation that immortalized cell lines be prepared from each participant to insure that adequate DNA will be available for all potential analyses and that a repository be established to handle cell lines and samples during and following the study. The patient consent forms have been modified to reflect this protocol change.

Research Goals and Scope

The NIDDK has formed a collaboration with the Laboratory of Genomic Diversity at the National Cancer Institute to establish cell lines from all FIND study participants and to establish a sample repository. Samples will be anonymized. The immortalized cells will provide a renewable, accessible source of DNA from all FIND study participants. This will enable multiple comparisons and analyses of genetic loci of interest in different subpopulations, increasing the utility of the research and the amount of available data from the study population. After completion of the study, provision will be made for sharing the genetic material with qualified investigators outside the FIND study who are conducting studies of the genetics of diabetic nephropathy.

5007 FAMILY INVESTIGATION OF NEPHROPATHY AND DIABETES: INCREASE MINORITY RECRUITMENT

FY 2001 Action

The NIDDK plans to expand the Family Investigation of Nephropathy and Diabetes (FIND) study to include more minority subjects, and to expand the FIND sample by addition of the well-phenotyped subjects from the African American Study of Kidney Disease and Hypertension (AASK) Trial.

Background

Kidney disease has a disproportionate impact on minority populations, especially African Americans and Native Americans. In 1996, the point prevalence rates of ESRD per million population, (adjusted for age and sex) were 3,404 in African Americans and 2,761 in Native Americans/Alaska Natives, compared to 754 in Caucasians, differences of 4.5 and 3.7 fold, respectively. African Americans develop end-stage renal failure at an earlier age than Caucasians; their mean age at ESRD incidence was 55.8 years compared with 62.2 in Caucasians. African Americans constitute almost 30 percent of prevalent ESRD patients, yet constitute only 12.6 percent of the U.S. population.

The FIND study was funded as a Cooperative Agreement (UO1) as the result of RFA DK-99-005. The aims of the FIND consortium are to identify genetic loci and ultimately genes that influence susceptibility and severity of diabetic nephropathy in Caucasian, African American, Hispanic, and Native American populations across the U.S. The Study Consortium consists of eight Participating Investigative Centers (PICs) and a Genetic Analysis and Data Coordinating Center. The External Advisory Committee for FIND has expressed concern that the susceptibility genes may differ in these sub-population groups, and that the sample size projected for African Americans may not offer adequate power to address analyses in this group. Given the high susceptibility of African Americans to kidney disease and the substantial health burden on this population, increased emphasis on this population was felt to be appropriate.

Research Goals and Scope

Several of the FIND participating investigative centers are able to expand minority recruitment by developing affiliations with minority institutions or inner city dialysis clinics. Complementary studies in the AASK clinical trial population are also proposed. This population is comprised of approximately 1,000 African American patients with renal insufficiency, most subjects with hypertensive nephrosclerosis. In this population, phenotypic parameters such as rates of progression of nephropathy and response to treatment are well characterized. Genetic analyses in this population will provide a comparison sample for analyses on diabetic nephropathy in patient populations of different ethnic backgrounds. Both family-based and mapping by admixture linkage disequilibrium approaches are planned.

5008 POLYCYSTIC KIDNEY DISEASE IMAGING STUDIES

FY 2001 Action

In FY 1999, NIDDK issued a request for applications (RFA), RFA DK 99-003, to encourage development of state-of-the-art imaging methods for polycystic kidney disease (PKD). The primary goal was to test whether imaging techniques can provide sufficiently accurate and reproducible markers of progression of renal disease in PKD to permit their use in clinical trials. In FY 2000, a consortium consisting of a Data Coordinating and Imaging Analysis Center (DCIAC) and four Participating Clinical Centers (PCCs) was created. In FY 2001, it is proposed to add ultrasound imaging methods and increased investment in image processing algorithms to this ongoing study.

Background

Several previous studies have established typical rates of decline of glomerular filtration rate (GFR) in PKD patients. Patients with PKD genotypes vary in their rate of progressive loss of renal function. Nevertheless, through much of the course of PKD, GFR is maintained and detectable decreases in GFR occur relatively late in the natural history of the disorder. Therefore, clinical investigation to attempt to alter the decline of GFR can only be undertaken late in the disease. Furthermore, although functionally a critical parameter, GFR is cumbersome to assess. Current state-of-the-art methods using magnetic resonance imaging (MRI) techniques with rapid image acquisition rates make possible high-resolution, three-dimensional images of the kidney. Semiautomatic image analysis algorithms also exist to determine renal size and renal parenchyma occupied by cystic structures. Some experience has been gained in establishing that repeat imaging of the same PKD patient, using these techniques, yields reproducible estimates of kidney size and proportion of kidney parenchyma occupied by cysts.

Ultrasound has the advantage of being more cost-effective and perhaps more acceptable by patients for repetitive studies, but the measurements may be less accurate and reproducible. Nonetheless, there is only very limited experience in applying these techniques to follow progression of the renal disease. The NIDDK Advisory Council has recommended addition of ultrasound methods to this study.

Research Goals and Scope

The focus of this initiative is investment in the groundwork that will facilitate the testing of interventional strategies to affect the course of renal disease progression. The primary objective of this consortium is to develop and test the accuracy and reproducibility of imaging techniques using MRI to monitor changes in cyst size and parenchymal involvement in a well-characterized cohort of patients with PKD. These PKD imaging studies are creating a unique opportunity for the application of improved imaging analysis algorithms for quantification of parameters related to kidney parenchyma status and cysts growth. With advice of the External Advisory Committee for this project and the NIDDK Advisory Council, an increase in resources to facilitate testing of the suitability

of ultra-sound techniques for these purposes and development of new image processing algorithms are proposed.

5009 MINORITY RECRUITMENT IN CHRONIC PROSTATITIS COHORT STUDY

FY 2001 Action

The Chronic Prostatitis Collaborative Research Network (CPCRN) will be expanded by addition of new clinical facilities to strengthen the recruitment of African American men with chronic prostatitis.

Background

Diseases of the prostate are a major health care burden for men. There is strong documentation that cancer of the prostate has a higher incidence in African American men. Although it has been suggested that the other two diseases of the prostate, benign prostatic hyperplasia (BPH) and chronic prostatitis (CP), are also more prevalent in African American men, these data are controversial and not well documented. Finally, it is unclear whether prostatitis increases the risk of malignancy in African Americans. Accurate determination of the incidence and natural history of the three main diseases of the prostate in various racial and ethnic populations is essential if insights into etiology, genetic susceptibility, and even treatment strategies are to be effectively developed.

In 1997, the NIDDK established and funded the CPCRN. The purpose of this network was two-fold: (1) to develop and follow a cohort of patients, who meet the NIDDK definition of CP, which can be utilized to characterize the clinical and epidemiological characteristics of this disorder, and (2) to start innovative therapeutic interventions in persons who meet the criteria for CP.

The CPCRN consists of six clinical centers and a data-coordinating center. Currently the CPCRN is addressing the first aim of the network--to develop and follow longitudinally a cohort of patients who meet defined clinical criteria. Patient recruitment into the centers has been excellent and has met or exceeded the established goals. However, the percentage of non-Caucasian, minority patients into the cohort has been less than five percent. This small percentage will not allow valid statistical determination of characteristics of chronic prostatitis in minority males. The initial selection of centers was based on ability to recruit patients with CP, and not on ability to access minority populations. In order to significantly increase enrollment of minority men into the cohort, it will be necessary to add an additional clinical center that has a demonstrated large population of minority men.

Research Goals and Scope

A clinical center located at the University of Mississippi in Jackson will be added to the CPCRN. This center has a large minority population and the principal investigator has a long-standing interest in the study of prostate diseases, including CP. Additional support will be provided to other centers with access to minority populations to provide support for personnel trained at minority recruitment. Patient recruitment at these clinical centers

will significantly increase the enrollment of minority patients in the CPCRn cohort and allow for statistically significant data analyses.

5010 INNOVATIVE THERAPEUTIC INTERVENTIONS FOR CHRONIC PROSTATITIS

FY 2001 Action

The purpose of this initiative is to support expansion of the Chronic Prostatitis Collaborative Research Network (CPCRN), a consortium of six clinical centers and a data coordinating center, to allow randomized, double-blinded, placebo-controlled trials of innovative approaches to the treatment of chronic prostatitis.

Background

Chronic prostatitis (CP) affects substantial numbers of adult men of all ages. It remains an enigmatic disorder for which effective treatment still is not available.

In 1997, NIDDK established and funded the CPCRN. The purpose of this network was two-fold: (1) to develop and follow a cohort of patients, who meet the NIDDK definition of CP, which can be utilized to characterize the clinical and epidemiological characteristics of this disorder and (2) to start innovative therapeutic interventions in persons who meet the criteria for CP. Through the CPCRN the NIDDK is testing diagnostic criteria that will clarify the definition of the disorder, and is following a cohort of patients to establish the natural history of this condition.

Analysis of the data from the cohort study has enabled the investigators to develop clinical and diagnostic criteria, which can uniformly characterize subjects for clinical treatment trials. In addition, the CPCRN has developed, validated, and published a symptom questionnaire, which has become the "gold standard" for evaluating treatment outcomes. With advice from CPCRN's External Advisory committee, it has been determined that in order to obtain statistically significant data from controlled clinical trials, the number of patients enrolled in the CPCRN must be increased significantly. To meet this increased enrollment, additional clinical centers must be added to the CPCRN.

Research Goals and Scope

During FY 2001, support will be provided to the CPCRN to allow the network to initiate randomized placebo-controlled clinical trials of therapeutic interventions. It is anticipated that the network will perform two or three pilot phase trials and one larger scale interventional trial, using the validated symptom questionnaire to provide the outcome measure.

5011 NATIONAL KIDNEY DISEASE EDUCATION PROGRAM

FY 2001 Action

NIDDK will begin planning a National Kidney Disease Education Program by sponsoring one or more planning conferences involving researchers, voluntary and professional organizations, health care providers and public health practitioners from academia, government, industry and groups representing diverse racial and ethnic populations. NIDDK will establish an executive committee to focus the program=s overall vision, goal, objectives, and direction, and to document the science base for an education program, including incidence and prevalence and the current environment for the diagnosis, prevention, and treatment of kidney disease. This program is part of NIDDK=s initiatives to reduce health disparities in ethnic and racial minority populations.

Background

The Council of American Kidney Societies--representing all major voluntary and professional organizations for kidney disease--has urged NIDDK to launch an education program to reduce the morbidity and mortality of kidney disease.

The health problems driving this interest include: (1) a striking, steady increase in the incidence of renal failure over the past two decades; (2) markedly higher rates of cardiovascular disease in people with renal insufficiency and renal failure; (3) high rates of "late diagnosis" of renal failure and consequently poor implementation of strategies to slow progression and prepare for renal replacement therapy; and (4) striking racial disparities in both the incidence of renal disease and the provision of optimum care. The current cost of treating people for kidney failure is an estimated \$16 billion.

On July 18, 2000, NIDDK convened an ad hoc Kidney Disease Education Task Force to obtain advice from a cadre of individuals with substantial expertise in health policy, education, and preventive medicine. The group identified areas of consensus that are ideal starting points for an education or outreach program, areas that may be ripe for consensus, and areas needing further research. The group placed high priority on developing outreach programs targeting high-risk minority populations, especially African Americans, Native Americans, and Hispanic Americans, using treatments for which scientific consensus already exist.

Research Goals and Scope

NIDDK will need to (1) further refine the science and organization of the education program; (2) seek broad public comment and establish partnerships; (3) prepare a strategic plan identifying baseline data, target audiences and plans to reach audiences; (4) establish a steering committee to extend the reach of the Executive Committee to ensure broad representation in planning and organizing the National Kidney Disease Education Program; and (5) implement strategies.

5012 URINARY INCONTINENCE AWARENESS CAMPAIGN

FY 2001 Action

The NIDDK=s National Kidney and Urologic Diseases Information Clearinghouse will launch a coordinated information program to reach African American and Hispanic and Latino American women, especially those with diabetes. Easy-to-read and culturally sensitive publications on bladder control that will be translated into Spanish include *Bladder Control for Women*; *Exercising Your Pelvic Muscles*; *Menopause and Bladder Control*; *Pregnancy, Childbirth, and Bladder Control*; *Talking to Your Health Care Team About Bladder Control*; *Your Body=s Design for Bladder Control*; and *Your Medicines and Bladder Control*. The NIDDK will also plan and develop additional culturally-sensitive messages and materials, working with public and private partners representing African Americans and Hispanic and Latino Americans to identify additional information needs of patients, families, and physicians. This program is one of NIDDK=s initiatives to reduce health disparities in ethnic and racial minority populations.

Background

An estimated 13 million people in the United States experience incontinence, but women are affected twice as often as men. Pregnancy and childbirth, menopause, and the structure of the female urinary tract account for this difference, but nerve damage from diabetes--a disease that affects 14 million Americans and disproportionately affects African American and Hispanic populations compared to Caucasians--is also a factor.

Women who have diabetes and damage to bladder nerves may not know when the bladder is full, and may have problems controlling the urge to empty the bladder and problems emptying it completely, allowing urine to leak and bacteria to grow more easily in the bladder and kidneys.

Research Goals and Scope

NIDDK will (1) extend its reach to public and private partners to develop culturally-sensitive materials about and approaches to bladder control; (2) attend additional professional meetings at which incontinence publications may be promoted; and (3) will promote the availability of free bladder control information in publications for minority audiences.

5013 ORGAN DONATION VIDEO FOR PIMA INDIANS

FY 2001 Action

NIDDK will support the development and production of a video that will include interviews with appropriate tribal members and Native American medical staff. The video must (1) educate tribal members about the fact that transplantation is a viable alternative to dialysis therapy; (2) raise awareness among the Gila River Community of the need for organs to alleviate the distress of patients on dialysis and to improve their quality of life; (3) address the cultural beliefs that may prohibit some American Indians from donating organs; and (4) demonstrate that Western and traditional methods of healing can complement each other to improve and extend life. A pamphlet that includes an organ donor card will provide a take-home message and an appropriate reminder to those who have seen the video.

Background

The NIDDK began working with Pima Indian volunteers in Phoenix, Arizona in the mid 1960s, after a health survey revealed an astonishing rate of type 2 diabetes in the tribe. Half of Pima Indians who are 35 and older have type 2 diabetes, the highest prevalence in the world. Pimas also develop diabetes at a much younger age than other populations, and the numbers of Pima children with the disease are increasing.

With the support of hundreds of Pima volunteers and the Indian Health Service, NIDDK's Phoenix Epidemiology and Clinical Research Branch has studied the origin, development and natural history of diabetes, its complications, and obesity for over 35 years. In addition to a clinical research center in Phoenix, NIDDK runs a diabetes clinic at Hu Hu Kam Memorial Hospital at Sacaton, Arizona, and has established dialysis centers on the Gila River Indian Reservation to treat kidney failure.

Research conducted in Phoenix and Sacaton established that the Pima Indians have 10 times the prevalence of type 2 diabetes found in Caucasian populations. These studies have also shown that diabetes, obesity, and kidney failure run in families, developing from genetic, prenatal, and environmental influences. In addition, doctors now recognize that high blood pressure predicts the complications of diabetes, and that lowering blood pressure may slow their onset and the progress of already existing diabetic kidney disease.

In spite of ongoing efforts to curb the incidence of kidney failure, prevalence remains high. The Hopi Indians have successfully raised awareness with a video and pamphlet encouraging organ donation. NIDDK staff and the Gila River Tribal Council hope to increase organ donation among the Pima Indians with a similar video and pamphlet.

Research Goals and Scope

There are striking racial and ethnic differences in the incidence and prevalence rates for kidney failure particularly among Native Americans, who are disproportionately affected by both diabetes and diabetic kidney disease. In Native Americans--as in the general U.S. population--diabetic nephropathy is the predominant cause of kidney failure. Greater access to kidney transplants for this population will substantially reduce the cost of medical care incurred with either hemodialysis or peritoneal dialysis and greatly improve their quality of life. Therefore, the goal of this initiative is to increase awareness of the need to donate organs and to encourage organ donation for transplantation in this population.

5014 DEVELOPMENT OF STRATEGIES FOR THERAPEUTIC INDUCTION OF FETAL GLOBIN GENES

FY 2001 Action

The purpose of this announcement is to stimulate new avenues of research into the developmental processes involved in the differential expression of globin genes. The emphasis is on understanding the mechanisms of regulation of fetal hemoglobin synthesis, and development of new approaches of stimulation of fetal hemoglobin in patients with Cooley's anemia and other beta chain hemoglobinopathies.

Background

Mutations in the globin gene cluster are among the most common inherited diseases in humans, leading to disorders that affect many individuals in the U.S. and around the world, such as sickle cell anemia and thalassemia (Cooley's anemia). Treatment for these disorders eventually may include both pharmaceutical agents and gene therapy. Some therapeutic approaches currently being studied are based on the fact that a number of naturally occurring mutations, such as HPFH and delta beta-thalassemia, are associated with significantly elevated levels of fetal hemoglobin (Hb F) in adult red blood cells. This increase in Hb F can be therapeutically beneficial, since it has been observed to modify the clinical severity of hemoglobinopathies associated with abnormal or deficient beta globin chains. A number of experimental drugs have been used successfully in some patients to increase the level of fetal hemoglobin in adults and some children. These studies have established the feasibility of this therapeutic approach to diseases with abnormal beta-globin production including sickle cell anemia and beta-thalassemia. However, not all patients respond to these treatments, their applicability to other disorders is not established, and the molecular and cellular basis for their mode of action remains unclear. Hence, further research is needed to broaden the range of possible therapeutic strategies for disorders of globin synthesis. The elucidation of precise molecular mechanisms responsible for increased Hb F production in these disorders could lead to the development of novel future therapeutic approaches to treat hemoglobinopathies.

Research Goals and Scope

The areas of research within this announcement include: (1) identification and characterization of trans-acting factors and other proteins involved in the developmental regulation of the fetal and embryonic globin genes; (2) identification and characterization of transcriptional co-activators of globin gene expression; (3) investigation of the mechanisms whereby protein acetylation and deacetylation participates in the activation and silencing of the fetal globin genes; (4) characterization of post-transcriptional mechanisms that may contribute to the developmental control of fetal globin genes; (4) study of the linkage between erythroid cell differentiation and the developmental control of the globin genes; (5) examination of the relevance of cell cycle control in globin gene expression; (6) examination of the relationship between globin gene expression and the

signal transduction mechanisms that are involved in erythroid cell maturation; (7) study of the molecular and cellular mechanisms, operative in various high Hb F syndromes, that can modulate the production of Hb F in all cells or increase the number of circulating red cells that contain Hb F (so-called F-cells); (8) mapping and cloning of non-globin-linked genes that may affect the expression of the fetal globin genes; (9) determination of the mechanism of action of drugs, such as hydroxyurea and butyrate, that affect HbF levels; (10) discovery of new classes of compounds that can induce fetal hemoglobin in cultures of primary erythroid cells and in animal models; and (11) development of new model systems to study the regulation of fetal globin genes.

5016 POLYCYSTIC KIDNEY DISEASE INTERVENTIONAL STUDY

FY 2001 Action

A new initiative for a multi-center interventional clinical trial is proposed to assess the best strategy for reducing morbidity and mortality in polycystic kidney disease (PKD). It is anticipated that a cohort of 2,000 patients will be enrolled in the study, which would begin a planning phase in FY 2001, and begin patient recruitment in FY 2002. The main issues to be addressed would be the optimum target levels for blood pressure control, and whether angiotensin-converting enzyme inhibitors offer superior benefit over other antihypertensive agents.

Background

A growing body of evidence supports the value of angiotensin-converting enzyme inhibitors (ACEi) for slowing the progression of kidney disease. Efficacy of these agents was first established for diabetic nephropathy in type 1 diabetes mellitus and then in type 2 diabetes mellitus. Efficacy in African Americans with hypertensive nephrosclerosis is being assessed in the African American Study of Kidney Disease and Hypertension (AASK) trial. A study of the early treatment of diabetic kidney disease with these agents, in adolescents and young adults with type 1 diabetes mellitus, is presently being conducted under the Renin Angiotensin System Study (RASS). There is some evidence for the effectiveness of these agents for patients with renal insufficiency and proteinuria from a number of smaller trials and meta-analyses. With regard to PKD, however, the data is conflicting, and no large trial has examined the effect of ACEi in this disease.

A Task Force meeting held in the fall of 1998, which was jointly supported by NIDDK and the Council of American Kidney Societies, identified intervention trials in high-risk groups of patients with progressive renal disease resulting from diabetes mellitus, hypertension, proteinuria, and PKD as one of the research priorities.

Research Goals and Scope

The objective of this initiative is to test the value of converting enzyme inhibitors for slowing progression of PKD. A prospective, randomized, multi-center clinical trial of approximately 2,000 patients is proposed. Converting enzyme inhibitors will be compared to blood pressure control with another agent, possibly with a two-by-two factorial design to incorporate level of blood pressure control. A time-to-event analysis would be used, with secondary outcome measures including cardiovascular outcomes. At the conclusion of the on-going PKD Imaging Study to Ascertain Progression (CRISP Study), the consortium will generate a special report with realistic estimates of the power of the imaging studies and other identified indices to predict progression of renal dysfunction.

The clinical trial is planned to consist of four sequential phases in which the experience and results from each phase will determine in what manner the next phase will be undertaken. Phasing of the study is envisioned as follows: Phase I--development of protocols and operations manual; Phase II--limited pilot studies; Phase III--full-scale clinical trial; and Phase IV--data analysis and reporting.

5018 ALTERNATIVE AND COMPLEMENTARY THERAPIES FOR SYMPTOMATIC BENIGN PROSTATIC HYPERPLASIA

FY 2001 Action

Alternative medicine approaches to the treatment of disease are particularly heavily utilized for conditions that affect quality of life. Many urological diseases fall within this category. The symptoms commonly associated with benign prostatic hyperplasia (BPH) have become a major target for utilization of alternative therapeutic agents. This initiative will develop a collaborative research group to assess the efficacy of widely used alternative and complementary strategies for treatment of BPH and to compare these agents with FDA-approved drugs for the treatment of this condition.

Background

Over 50 percent of men 50 years of age or older have symptoms attributable to BPH. BPH has been shown to have a significant negative impact on patient-reported quality of life and psychological well-being, and can result in life-threatening obstruction of the lower urinary tract. The condition accounts for at least 1.7 million office visits per year, and the costs associated with treatment of this condition have been estimated to exceed \$4 billion per year. Surgical treatment of BPH is second only to cataract surgery as the most-common surgical treatment performed in the male Medicare population.

The use of alternative therapeutic approaches for the relief of the symptoms of BPH is increasing very rapidly. Two plant-derived therapies are being widely used, extracts of *Pygeum africanum* and saw palmetto berry. In 1996, saw palmetto was the ninth most common herbal remedy sold in the U.S.; in 1997, it was the fifth most common.

Physicians are very reluctant to either recommend or discuss treatment with these agents because of the lack of high quality clinical trials, and are often unaware that their patients are taking these compounds. A recent survey has shown that in selected clinical practices up to 90 percent of men are either using or have used alternative medicine to treat BPH symptoms. A recent editorial in the New England Journal of Medicine highlighted the need for further testing of herbal remedies sold with the ambiguous claim of promoting prostate health. The editors concluded that "alternative therapies should be subjected to scientific testing no less rigorous than that required for conventional treatments."

There is little rigorous published evidence to demonstrate that these therapies have any effect on either the pathology of the prostate or bladder, quality of life, or the symptoms commonly associated with BPH. In addition, there are no data on the safety of these therapies. Although studies reporting their efficacy exist, the work does not meet the rigorous criteria of randomized clinical trials. Nonetheless, there is a substantial body of anecdotal evidence for symptom relief, and some uncontrolled trials suggesting changes in pathology and serum hormone levels. It has been suggested that these agents might have a different mechanism of action from current FDA-approved regimens, and might

enhance or complement the effect of the currently utilized FDA-approved medical therapies. The anecdotal evidence that these treatments have a positive effect on quality of life, and decrease prostate hyperplasia deserves rigorous examination in a controlled clinical trial.

Research Goals and Scope

The goal of this initiative is to determine the clinical and physiological effect of the most common phytotherapy agents used for the treatment of the symptoms of BPH. A consortium of basic and clinical investigators will be established to evaluate which symptoms associated with BPH are modified by these agents, the duration of the effect, the effect on prostate tissue and the urinary bladder (as determined by urodynamics profiles), and serum hormone and prostate markers such as prostate-specific antigen and testosterone.

Accepted quality of life measures, such as the American Urological Association symptom score, and objective measures such as trans-rectal evaluation of prostate volume, urodynamics, and prostate biopsy will be utilized to assess effect of the two most common phytotherapeutic agents, alone or in combination with pharmacological intervention.

5020 COMPLETION OF THE AFRICAN AMERICAN STUDY OF KIDNEY DISEASE AND HYPERTENSION (AASK) CLINICAL TRIAL

FY 2001 Action

The NIDDK proposes to extend the full-scale phase of the African American Study of Kidney Disease and Hypertension (AASK) clinical trial by one year. This extension will enable the participating clinical centers to complete data collection on the patients randomized into the study. At the conclusion of the data collection phase, the Data Coordinating Center will, in collaboration with the investigators, commence the final data analyses. The results of the primary end-point analysis will then be presented for review and publication.

Background

African Americans are disproportionately affected with end-stage kidney failure (ESRD). Whereas they constitute approximately 12 percent of the U.S. population, they comprise 32 percent of the prevalent ESRD population. Diabetes mellitus is the predominant cause of ESRD in the U.S. population. However, hypertension is the most frequently reported cause of ESRD in African Americans. In 1990, the NIDDK launched an initiative to investigate the underlying cause, and to study mechanisms that could slow progression of hypertensive kidney disease in African Americans. An important component of this initiative is the African American Study of Kidney Disease and Hypertension (AASK) Clinical Trial.

Between 1991 and 1994, the NIDDK supported ten clinical centers, including all the predominantly black medical schools, to conduct a pilot clinical trial during which they were to develop and test a protocol to be used for the full-scale clinical trial. Following the successful completion of the pilot study, 20 clinical centers and a Data Coordinating Center were funded in July 1994 to carry out the full-scale clinical trial. The twenty-first clinical center was added in June 1996. The study is designed to test two levels of blood pressure, a usual blood pressure level (Mean Arterial Pressure, MAP 102-107 mm Hg) versus a lower blood pressure level (MAP 92 mm Hg). The study also addresses the effect of three major classes of antihypertensive drugs, beta blockers versus ACE inhibitors versus calcium channel blockers. The NIDDK is collaborating with the pharmaceutical industry in the conduct of the clinical trial to the extent that industry is providing the randomized (primary) agents for support of the study. The beta blocker, Toprol, is provided by ASTRA, USA; the ACE Inhibitor, Ramipril, is provided by Marion Hoechst Roussel (now marketed by King Pharmaceuticals); and the calcium channel blocker, Amlodipine, is provided by Pfizer Inc. The step three drug, Doxazosin, is also provided by Pfizer Inc. The three research hypotheses being tested by the study include: (1) will there be a difference in the rate of progression of kidney disease (assessed by glomerular filtration rate) between control group (MAP 102-107, beta blocker) and the intervention group (MAP 92 mm Hg, ACE Inhibitor, calcium channel blocker); (2) will there be a difference between treatment groups in the mean rate of decline in renal

function (assessed by GFR) during the chronic phase; and (3) will there be a difference between treatment groups in the level of renal function (assessed by glomerular filtration rate) at the end of the study follow-up period.

The projected recruitment and randomization period was estimated to be two years. However, because of the slow accrual rate, additional 14 months was required to complete recruitment.

Research Goals and Scope

The additional one-year extension of funding of the clinical centers will enable completion of data collection during the follow-up portion of the clinical trial. Data analysis of the primary end-points will commence at the conclusion of the follow-up period.

5021 COMPLETION OF THE HEMODIALYSIS (HEMO) STUDY

FY 2001 Action

The Hemodialysis (HEMO) Study is an ongoing multi-center, randomized clinical trial evaluating the effects of dialysis dose and membrane flux on morbidity and mortality among maintenance hemodialysis patients. Additional support will be provided in FY 2001 to permit the investigators to conduct patient closeout and complete data collection.

Background

In response to the high mortality rate observed among maintenance hemodialysis patients, the NIDDK initiated a multi-center randomized clinical trial, the HEMO Study, in 1995. Because information from observational studies suggested that the dose of dialysis is an important factor in patient survival, the trial is comparing a higher than usual dialysis dose with a usual dose on patient survival and morbidity, including hospitalization. In addition, the effect of high- versus low-flux dialysis membranes on patient outcomes is also being examined. The trial is progressing well, and the External Advisory Committee is scheduled to meet in November 2000 to again consider the outcome of the trial and perform their usual evaluation of the data pertaining to the safety of the interventions.

Research Goals and Scope

The clinical trial is reaching its later stages. Recruitment of participants will be completed in the fall of 2000 and follow-up will terminate at the end of 2001. Currently, funding for the trial terminates on August 31, 2001. At the June 2000 meeting of the NIDDK Advisory Council, an extension of the project period and additional funding for the trial was approved. This is required to complete patient follow-up, inform the study participants of the results of the trial, and to permit the investigators to verify data collected during the final months of the trial.

5022 EXPANSION OF URINARY INCONTINENCE TREATMENT NETWORK CLINICAL CENTERS (RFA DK-99-001)

FY 2001 Action

In FY 2000, the NIDDK began the development of a Urinary Incontinence Treatment Network (UITN) by supporting four clinical centers and one statistical center. In FY 2001, the number of clinical centers will be expanded to allow additional important clinical studies.

Background

Urinary incontinence is a common problem. The factors influencing a patient's decision to seek care and the criteria by which the clinician selects therapy are not uniform. There are numerous options available for the treatment of urinary incontinence, including surgery, pharmaceuticals, behavioral modification, and prostheses. Frequently, a combination of these therapies is utilized. Most of the literature on surgical intervention supports the conclusion that there is marked improvement in continence during the immediate and short-term post-operative period. There are, however, very few well-designed, long-term observational studies that document the outcomes of surgical interventions over a longer period. The clinical studies reported to date suffer from a number of methodological shortcomings, including brief follow-up, inadequate sample size (and thus low statistical power), uncertain diagnostic criteria for patient selection and outcome assessment, absence of documentation of complications, and large numbers of patients lost to follow-up (thus introducing possible bias into results).

In FY 2000, NIDDK established the UITN with the goal being to ascertain the long-term effectiveness of the common surgical approaches for the treatment of urinary incontinence in women. The currently funded centers will convene as a steering and planning committee to develop a protocol, quality of life indicators, and diagnostic and clinical enrollment criteria. The four current centers do not have either adequate enrollment potential or access to ethnic/racial diversity to allow for statistical significance in interpretation of patient derived data.

Research Goals and Scope

During FY 2001, additional clinical centers will be added which will allow for adequate patient enrollment to meet the statistical needs of the study design.

DIVISION OF KIDNEY, UROLOGIC AND HEMATOLOGIC DISEASES
Conferences and Workshops

Preparing for a Research Career in Clinical Nephrology
Bethesda, MD
September 2000

Highly trained clinical researchers are needed to translate the many profound fundamental science developments and discoveries into clinical settings. Unfortunately, training in clinical research is often fragmented. NIDDK is launching an annual training series that will focus on building the skills needed for a successful clinical research career in nephrology. The workshop will feature state-of-the-science lectures, mentored training sessions in trial design, and a mock NIH study section. Attendees will be expected to participate in a journal club, design a clinical trial, and review clinical trial grants at a mock study section. The goal of this program is to better train participants so that they might more effectively compete for research funding.

International Research Symposium on Interstitial Cystitis and Bladder Research
Minneapolis, MN
October 19-20, 2000

This meeting will present new findings on the cell biology, neurobiology, genetics and immunology of the urinary bladder, as well as reports of recent findings on biomarkers in interstitial cystitis and other bladder disorders. Descriptions of potentially associated syndromes will be presented, as well as novel therapeutic approaches.

International Prostatitis Collaborative Meeting
Bethesda, MD
October 24-25, 2000

The purpose of this meeting is to review current advances in the basic and clinical science of chronic prostatitis and to continue development of an international cohort of patients who fit the NIDDK criteria for the disease. This meeting will permit international discussion and collaboration in research on chronic prostatitis.

Task Force for Interventional Trial in Pediatric Focal Segmental Glomerulosclerosis
October 2000

Focal Segmental Glomerulosclerosis (FSGS) is an irreversible glomerular process with steroid-resistant nephrotic syndrome with a great risk of progression to end stage renal disease. Treatment interventions consist of corticosteroids; alternative therapy includes alkylating agents, Levamisole, CsA, Chlorambucil, and others. This task group will gather

information on the criteria for, and nature of interventions for a clinical trial on FSGS of idiopathic origin in children.

Science of Placebo: Toward an Interdisciplinary Research Agenda

Bethesda, MD

November 19-21, 2000

In cooperation with the National Center for Complementary and Alternative Medicine, the National Institute of Diabetes and Digestive and Kidney Diseases is holding a workshop entitled "Science of Placebo: Toward an Interdisciplinary Research Agenda." This meeting will bring together psychologists, sociologists, biologists, ethicists, clinical trialists, and statisticians to examine the theory behind, occurrence, and analysis of the placebo effect in a variety of research settings, including randomized clinical trials. A series of research recommendations will be made from breakout sessions. A book containing manuscripts of the presentations is being planned. The meeting will be co-sponsored by over a dozen NIH institutes and offices.

Working Group to Devise Standards for Microarray Experiments

Bethesda, MD

November 2000

This Working Group will devise standards for microarray experiments including minimal elements of annotation, microarray data representation in XML, ontologies, normalization/standardization, and queries to public databases. The Group will focus on elements needed to describe the sample being tested and will derive a broad overall framework (organism, anatomy, developmental stage, treatment, phenotype, pathology, history, etc.).

International Workshop on Oxalate Stone Disease

Bethesda, MD

November 2000

This workshop will provide a forum for new findings in oxalate kidney stone disease, including new animal models, contributions of oxalobacter, tissue response to stone formation, genetics, and clinical issues. Gene therapy, stem cell biology, and contributions to therapy, and new approaches in liver transplantation will also be discussed.

Workshop on Renal Genomics in the Post-Genomic Era

Bethesda, MD

Spring 2001

This workshop will present state-of-the-art genomic and gene profiling methods that can be used to simplify gene discovery in the post-genome era. The workshop will also discuss methods for studying gene regulation, transcription, and function using advances gene profiling and proteomic approaches.

Workshop on Non-invasive Measurement of Iron
Bethesda, MD
April 2001

There is a pressing need to be able to perform non-invasive measurements of body iron stores, in order to diagnose and monitor treatment for patients with transfusion-related iron overload and possibly for individuals with hemochromatosis mutations. A one-day workshop is planned to evaluate a number of potential methods for the noninvasive measurement of body iron load, including SQUID and MRI. The workshop is intended to advance the technology and to assist the NIDDK in making decisions on needed initiatives in this research area.

Workshop: Strategies to Reduce the Risks of Progression of Chronic Kidney Disease
May 2001

After initiation of renal injury several factors, both genetic (physiologic) and environmental, play a role in sustaining progression to severe and/or terminal renal failure. The physiologic/environmental factors include uncontrolled blood pressure, poor glycemic control, renal hemodynamics, prostaglandins, and abnormal lipids. Furthermore, as renal disease progresses, patients are at risk of developing co-morbid conditions, such as cardiovascular disease and malnutrition. Early recognition of the presence of renal disease and reasonable intervention strategies will reduce renal disease progression, and improve other health parameters. Primary care physicians, nephrology health care team, and the public need to be informed and work together to reduce renal disease progression and improve general health. The proposed workshop will bring together a multi-disciplinary team and experts to formulate strategies to: (1) detect early the presence of renal dysfunction, and define factors that promote progression of the kidney disease; (2) increase awareness about the high risk of cardiovascular disease and malnutrition, and define specific approaches to improve risk management; (3) improve preparation of patients with severe renal insufficiency for renal replacement therapy; and (4) reduce racial and ethnic disparities in the incidence and care of kidney disease.

Progress Review Group for Bladder Research

A Progress Review Group for Bladder Research is being planned. The goals are to evaluate the NIDDK and NIH portfolio in bladder research and to develop the future research agenda for bladder research at NIDDK and NIH. An initial advisory board will meet in the fall/winter of 2000 to assist in organizing this effort, identifying potential participants, and planning a larger meeting to be held later in 2001.